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Contrast Echocardiography in Coronary Artery Disease

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1. Introduction

Conventional echocardiography is widely used and well documented in evaluation of patients with stable and unstable coronary artery disease (Mollema et al., 2009). In particular, assessment of left ventricular function, volumes and ejection fraction adds important prognostic information in individual patients. In addition, echocardiography may detect any concomitant valvular heart disease as well as acute complications in unstable coronary syndromes. Stress echocardiography has through several studies established its role in diagnosis of stable coronary artery disease and assessment of myocardial viability (Sicari et al., 2008).

However, introduction of ultrasound contrast agents and contrast specific imaging modalities have significantly improved the usefulness of echocardiography in diagnosis and assessment of coronary artery disease (Dijkmans et al., 2006). Indications for use of ultrasound contrast are implemented in guidelines for assessment of left ventricular function at rest and during stress echocardiography (Senior et al., 2009; Mulvagh et al., 2008). Ultrasound contrast is recommended for assessing left ventricular ejection fraction at rest when image quality is suboptimal and for stress echocardiography when the endocardial boarder is not visualized in 2 or more left ventricular segments (Senior et al., 2009; Mulvagh et al., 2008).

In contrast echocardiography regional myocardial function and perfusion may be assessed simultaneously, thereby optimizing the non-invasive diagnostics of coronary artery disease. The incremental value of assessing myocardial perfusion in diagnosing coronary artery disease is emphasised by the ischemic cascade (Fig. 1), demonstrating that hypoperfusion precedes functional impairment, ECG changes, symptoms and myocardial necrosis as depicted in Fig.1. (Crossman, 2004; Leong-Poi et al., 2002).

Diagnosing distribution and extent of myocardial ischemia by contrast echocardiography can give information on the total ischemic burden and has become a supplemental tool in evaluation of the physiological impact of an angiographic coronary artery stenosis. Consequently, myocardial perfusion assessment by contrast echocardiography may also be used for risk prediction in patients with known coronary artery disease and in prioritizing the need for urgent revascularization among patients with acute coronary syndromes (Jeetley et al., 2007; Rinkevich et al., 2005; Lønnebakken et al., 2011). It has the potential to become a future tool to tailor and evaluate the effect of treatment on myocardial perfusion in patients with different clinical syndromes of coronary artery disease. Furthermore,

contrast echocardiography can be used to identify myocardial ischemia in patients with non-obstructive coronary artery disease i.e. microvascular disease which cannot be diagnosed by routine coronary angiography.

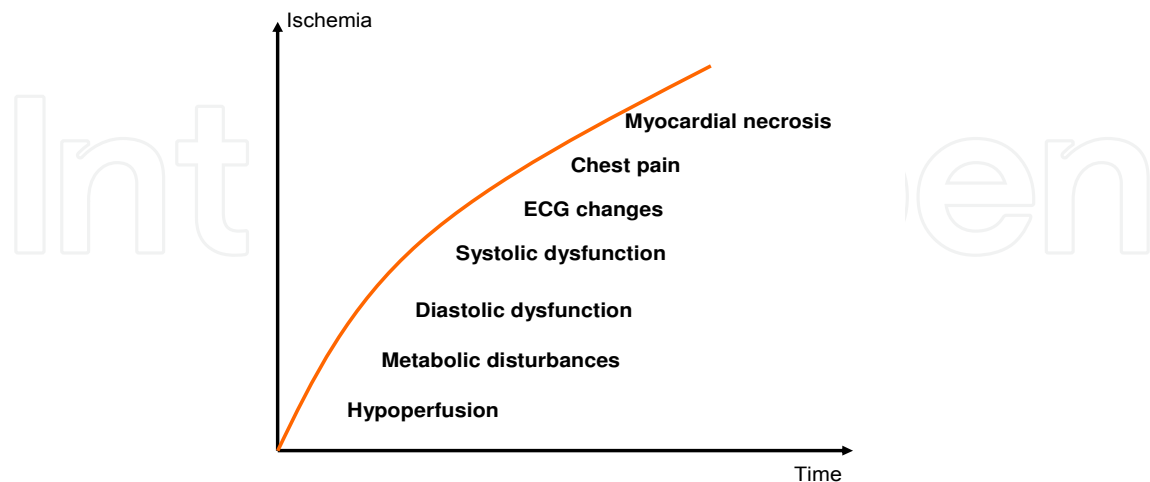


Fig. 1. The ischemic cascade

2. Methodology

Contrast echocardiography has several advantages compared to other non-invasive imaging techniques like cardiac magnetic resonance imaging and cardiac computer tomography. First, it can be performed without the radiation exposure of computer tomography and without the potential nephrotoxicity of the gadolinium contrast agent necessary to assess myocardial perfusion by magnetic resonance imaging. Second, it can be performed bed-side and give immediate answers to important clinical questions in management of patients with known or suspected coronary artery disease. Contrast echocardiography requires intravenous administration of a second or third generation ultrasound contrast agent during contrast specific ultrasound imaging.

2.1 Ultrasound contrast agents and imaging modalities

Ultrasound contrast agents consist of microbubbles with an inert gas core surrounded by a shell. Due to the microbubble size and stability, they can pass the pulmonary circulation without destruction and intravenous administration as bolus dosages or continuous infusion can therefore be used (Senior et al., 2009). Importantly, the contrast microbubbles act as isolated intravascular tracers and are therefore ideal for perfusion assessment. Future possibility of targeting contrast microbubbles against specific disease processes, including inflammation in unstable plaque, activated platelets in thrombus formation or against factors involved in angiogenesis may allow even more specific diagnoses (Kaufman & Lindner., 2007; Chadderdon & Kaul., 2010).

Ultrasound contrast agents in coronary artery disease have been shown to be safe, but allergic anaphylactic reactions have been observed (Senior et al., 2009; Wei et al., 2008). Therefore, patients should be observed closely with continuous recording of heart rhythm and frequent measurement of blood pressure during contrast echocardiography and for at least 20 minutes after the examination. Emergency equipment should always be available in the examination room during contrast echocardiography. Contrast echocardiography has

few absolute contraindications, except for known allergy against the contrast agent. However, caution and close observation should be performed in patients with unstable coronary artery disease or decompensated heart failure. Ultrasound contrast agent should also be used with caution in patients with severe pulmonary disease. The gas in the contrast microbubbles is excreted through the lungs, and in patients with severe pulmonary disease, clearance is delayed, causing increased halftime of the gas in the circulation. In patients with mechanical valve prosthesis contrast echocardiography should be avoided due to extensive destruction of contrast microbubbles by the prosthesis. An overview of current commercially available ultrasound contrast agents is given in Table 1.

Contrast agents	Gas core	Shell
SonoVue	Sulphur hexafluoride	Phospholipid monolayer
Luminity/Definity	Perflutren	Phospholipid monolayer
Optison	Perflutren	Albumin
Albunex	Air	Albumin

Table 1. Gas core and shell composition in ultrasound contrast agents available for clinical use

Contrast microbubbles have unique acoustic properties when exposed to ultrasound. At very low mechanical index, the ultrasound microbubbles have a linear response to the ultrasound exposure. At low mechanical index (MI 0.08-0.3) the ultrasound microbubbles start to oscillate giving rise to a non-linear response contrasting the linear response of the myocardial tissue at low mechanical index. Contrast specific ultrasound imaging modalities remove the linear tissue response and enhance the contrast microbubble response. Different techniques may be used to emphasize the contrast microbubbles acoustic signals and to filter the tissue signals, the main techniques being power modulation, pulse inversion or coherent contrast imaging.

Low-mechanical index imaging is the most commonly used modality, often combined with a high energy ultrasound flash causing microbubble destruction, known as destruction-replenishment imaging or flash imaging (Fig. 2). By this technique real-time contrast echocardiography with simultaneous assessment of myocardial function and perfusion can be performed.

High mechanical index imaging causes microbubble destruction. By high mechanical index triggered imaging, myocardial perfusion can be assessed, but myocardial function can not be assessed simultaneously using this imaging modality. The advantage of this imaging modality is a better reproducibility for quantification of myocardial perfusion.

2.2 Performance and image interpretation

Ultrasound contrast may be used to improve endocardial border delineation, a technique known as left ventricular opacification (LVO) (Fig.3) (Chahal & Senior, 2010), which has been demonstrated to optimize assessment of left ventricular volumes and ejection fraction by echocardiography compared to cardiac magnetic resonance imaging, the current gold standard (Malm et al., 2006). In patients with poor acoustic windows, left ventricular ejection fraction is often underestimated if ultrasound contrast is not used (Kurt et al., 2009; Plana et al., 2008). Using ultrasound contrast significantly improves echocardiographic reproducibility and accuracy in patients with poor acoustic windows, and use of contrast echocardiography in such cases for accurate assessment of left ventricular ejection fraction is

Low mechanical index imaging with destruction replenishment

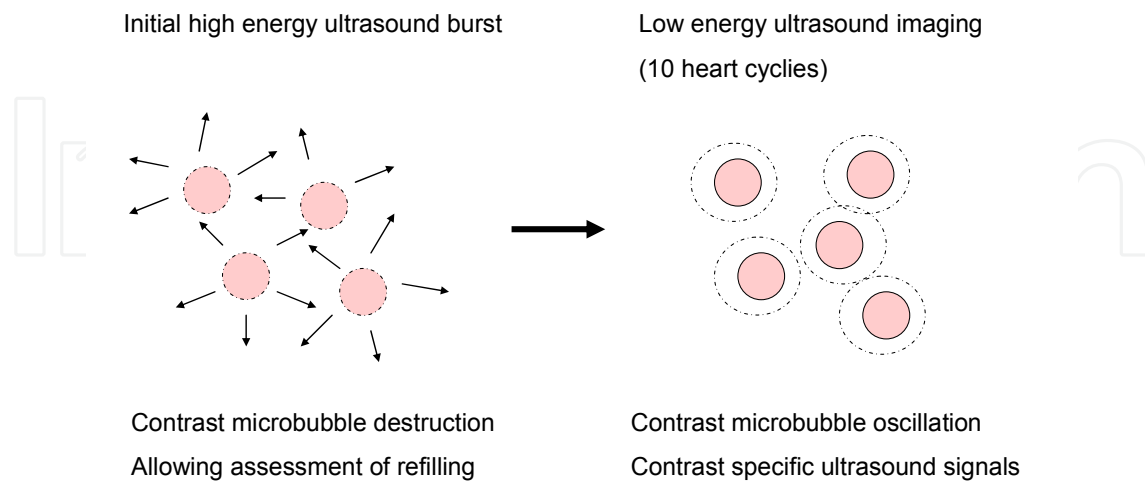


Fig. 2. Destruction replenishment contrast echocardiography, where a high energy ultrasound burst causes ultrasound microbubble destruction, followed by low mechanical index ultrasound imaging assessing only the non-linear ultrasound reflection from oscillating contrast microbubbles by contrast specific ultrasound imaging allowing assessment of contrast enhancement and hence myocardial perfusion.

recommended in current guidelines (Senior et al., 2009). Similarly, during stress echocardiography, adding ultrasound contrast allows a complete evaluation of wall motion in all myocardial regions in almost every patient (Hoffmann et al., 2007).

In a study of 632 patients with poor acoustic windows, adding ultrasound contrast not only avoided the need of further expensive and time consuming examinations but also had direct impact on patient's treatment (Kurt et al., 2009).

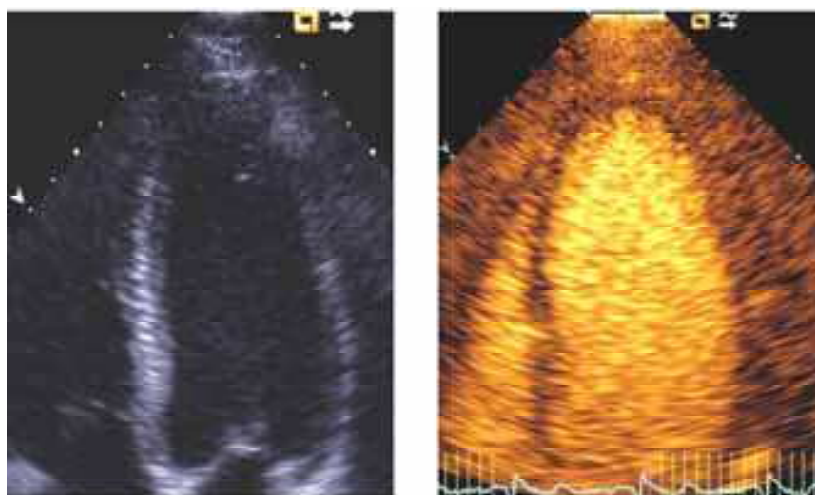


Fig. 3. Left ventricular opacification (LVO) by contrast echocardiography illustrating the improved endocardial border delineation in particular in the apical part of the left ventricle in an apical 4-chamber view compared to conventional echocardiography.

In myocardial contrast echocardiography (MCE), contrast is not only used for enhanced endocardial border delineation, but also for assessment of regional perfusion with high spatial and temporal resolution (Fig. 4) (Elhendy & Porter., 2005). MCE has the potential to significantly improve non-invasive evaluation of coronary artery disease (Elhendy et al., 2004; Lønnebakken et al., 2009). Contrasting other non-invasive imaging modalities, MCE visualizes the capillary filling in the myocardium and can give information on regional myocardial perfusion including subendocardial hypoperfusion, which is the first sign of ischemia (Dijkmans et al., 2006). Consequently, MCE increases the sensitivity to detect ischemia. In addition, myocardial microvascular integrity can be evaluated and myocardial viability assessed.

Myocardial contrast echocardiography is mainly performed using apical 4-chamber, apical 2-chamber and apical 3-chamber views. Parasternal imaging is more difficult due to contrast attenuation, but additional parasternal long- and short axis images may be useful in individual patients, in particular at peak stress. By combining rest-imaging with an exercise or pharmacological stress test, myocardial function and perfusion can be evaluated not only at rest but also during stress, which is particularly important in diagnosis of stable coronary artery disease, evaluation of viability and in evaluating the result after coronary revascularization. Image analysis is performed using a standardized 17-segment left ventricular model, in which the different left ventricular segments are assigned to the three main coronary arteries using a standardized scheme (Fig. 5) (Lang et al., 2006). However, the considerable variation in coronary artery anatomy must be taken into account when comparing MCE results to coronary angiography.

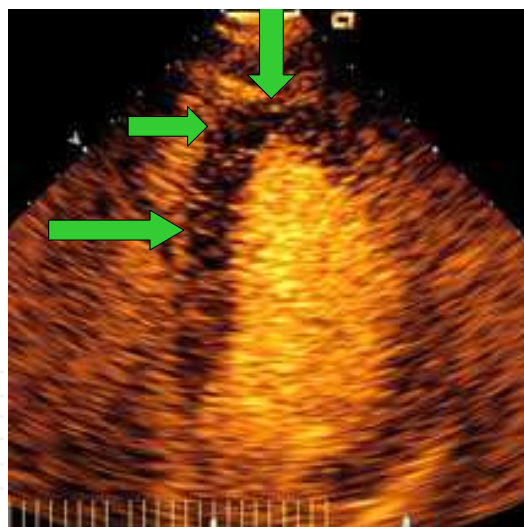


Fig. 4. Myocardial contrast echocardiography with low mechanical index demonstrating the delayed contrast enhancement in the distal septum and apex of the left ventricle (green arrows) compared to the proximal septum and lateral wall in an apical 4-chamber view.

2.2.1 Wall motion scoring

Myocardial regional function or wall motion is evaluated from active myocardial thickening and scored according to current guidelines as normal (1), hypokinetic (2), akinetic (3) or dyskinetic (4) (Sicari et al., 2008). In addition, there should be a further increase in wall thickening during stress testing to be scored as normal. In viability assessment, an akinetic

segment that starts to function at low stress level but ceases to function again at higher stress level is indicative of viable myocardium with ischemia, known as the biphasic response, typically for stunned or hibernating myocardium. Such findings indicate that the regional myocardial function will improve from revascularisation. Akinetic myocardial segments that remain akinetic during stress indicate infarct scarring which will not benefit from revascularization.

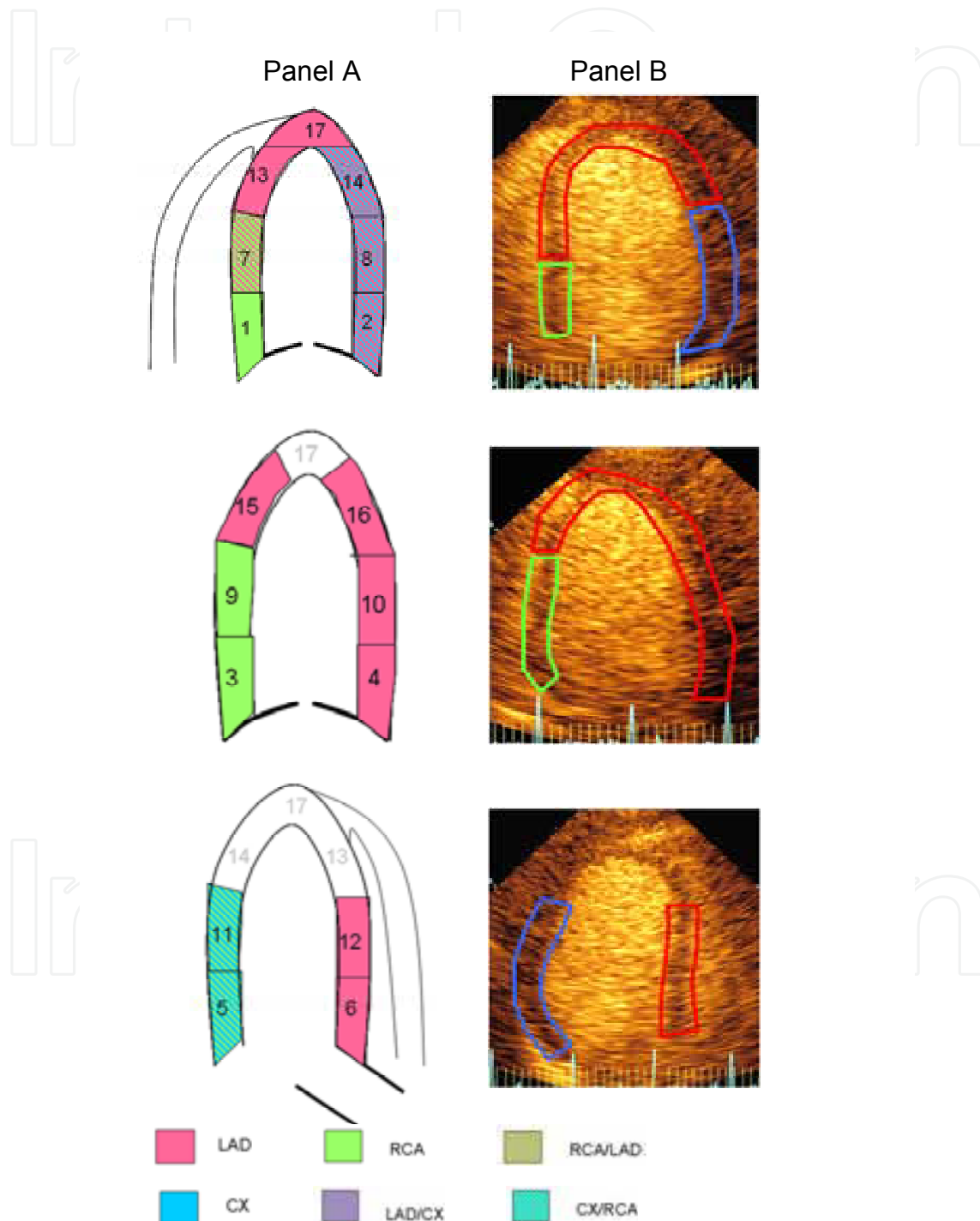


Fig. 5. Left ventricular model for wall motion and perfusion scoring during contrast echocardiography and standardized attribution to the main coronary arteries.

2.2.2 Perfusion scoring

Regional perfusion scoring is based on visual evaluation of contrast enhancement in the myocardium. At rest the myocardium should be filled with contrast during 5 heart beats, while at peak stress the myocardium should be filled in 1-2 heart beats. Delayed enhancement is consistent with hypoperfusion or ischemia, while lack of enhancement is consistent with myocardial fibrosis or infarct scarring. However, artefacts like contrast destruction in the near field may cause false perfusion defects in the apical myocardium, while attenuation may cause false perfusion defects in the basal parts. In addition, perfusion defects in thin fibrotic myocardium may be underestimated because of shine-through effect. In patients with stable coronary artery disease, perfusion scoring by contrast stress echocardiography has been demonstrated to identify prognostically important angiographic coronary artery disease (multivessel disease and proximal stenosis in the left anterior descending artery) significantly better than wall motion scoring (Lønnebakken et al., 2009). However, anatomical variations in coronary anatomy as well as collateral circulation and coronary artery bypass grafting will influence the perfusion area of the individual coronary artery. Therefore, except for stenosis in the proximal left anterior descending artery, the anatomic culprit lesion can usually not be identified by MCE.

2.2.3 Quantification of myocardial perfusion

Quantification software assessing contrast enhancement from increase in video intensity over time has been developed (Agati et al., 2005). From quantitative analysis, typical contrast enhancement curves can be obtained for blood flow velocity (β), perfusion rate ($A \times \beta$), refilling time (rt) and total blood volume (A) (Fig.6.). In normally perfused

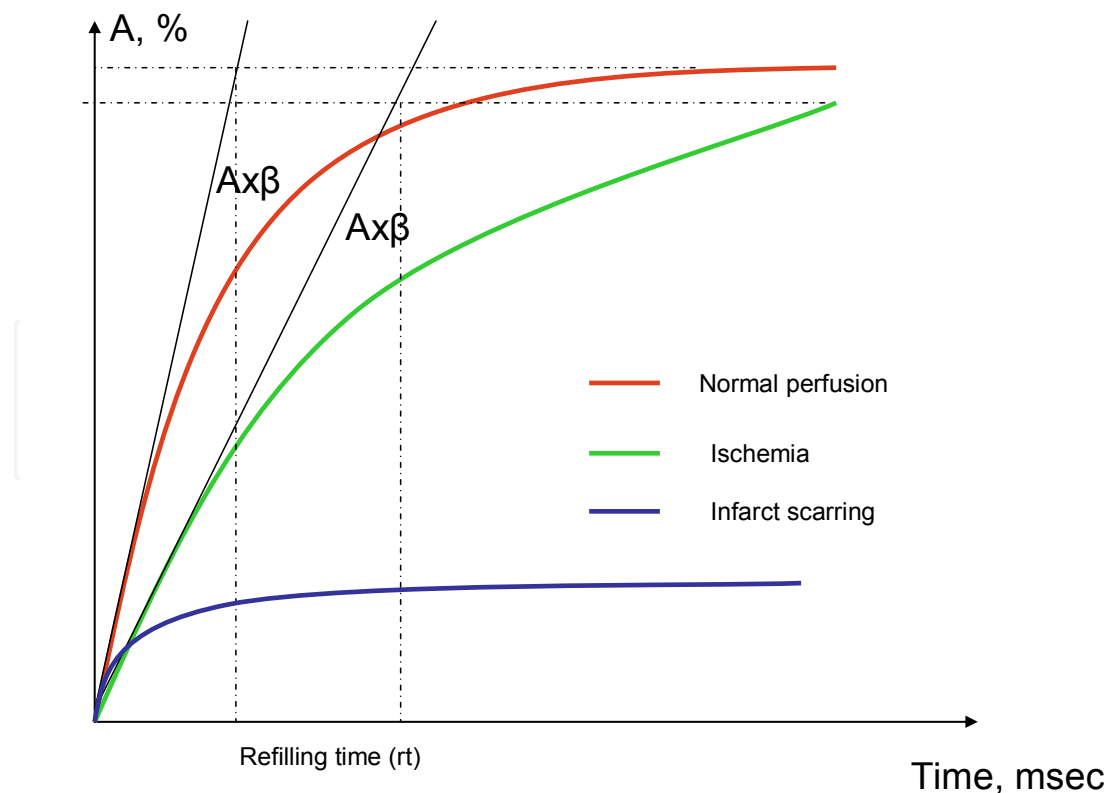


Fig. 6. Contrast enhancement curves: for normally perfused myocardium (red curve), ischemic/hypoperfused myocardium and for infarct area (blue curve), respectively.

myocardium, the blood flow velocity is about 0.5 ml/s and the peak intensity level is rapidly reached (Fig.6 red curve). In ischemic myocardium, both the blood flow velocity and perfusion rate are reduced, the refilling time is increased while the total blood volume remains normal (Fig.6 green curve). This contrasts the reduced total blood volume characterizing the myocardial contrast enhancement in infarcts scarring and myocardial fibrosis (Fig.6 blue curve) (Wei et al., 1998; Toledo et al., 2006).

Using quantification, it is theoretically possible to compare myocardial perfusion in different regions and settings. However, previous studies have demonstrated that it is difficult to compare between different patients due to large interindividual variation. In a study of 20 healthy subjects with normal wall motion and coronary angiography, both considerable inter-individual and also inter-regional variability in perfusion parameters were noted, suggesting that quantitative perfusion parameters currently are best suited for within patient repeated assessment, for instance during stress testing (Malm 2005). This was confirmed in a follow-up study of patients who underwent quantitative contrast stress echocardiography prior to and 9 months after percutaneous coronary revascularization. In this study, stress induced perfusion but not absolute perfusion parameters were improved in patients with angiographic successful result, while a lack of improvement in stress induced perfusion was associated with angiographically confirmed restenosis irrespective of patient symptoms (Lønnebakken et al., 2009). However, standardisation and assessment of optimal cut-off values for myocardial perfusion has to be derived from larger trials before quantification of myocardial perfusion can be used in clinical assessment of coronary artery disease (Abdelmoneim et al., 2009).

3. Clinical applications

Contrast echocardiography has documented important clinical impact on diagnosis, risk prediction and follow-up of patients with different clinical syndromes of coronary artery disease as well as in detection of thrombotic complications in patients with ischemic heart disease. In addition assessing the total ischemic burden and viability by contrast echocardiography adds prognostic information in individual patients.

3.1 Stable coronary artery disease

Diagnosing stable coronary artery disease may be challenging, in particular since atypical symptoms are not uncommon. The most used diagnostic test in coronary artery disease, the exercise electrocardiogram, is associated with a low accuracy to detect significant angiographic coronary artery disease. Invasive coronary angiography is according to current guidelines the diagnostic gold standard. However, it is invasive and associated with potential risk for severe complications and allergic reactions, and includes radiation exposure. Furthermore, coronary angiography does not give information on the functional importance of a coronary stenosis. Stress echocardiography has an overall diagnostic sensitivity of 85% and specificity of 90% in detecting significant angiographic coronary artery disease from meta-analyses (Senior et al., 2005; Picano et al., 2008). However, in 33% of patients referred for conventional stress echocardiography the image quality does not allow adequate evaluation. By adding ultrasound contrast during stress echocardiography almost all patients can be satisfactorily examined by stress echocardiography and by simultaneous assessment of both myocardial function and perfusion (MCE) the sensitivity of detecting significant angiographic coronary artery stenosis may be increased to 90% but the specificity is reduced (Senior et al., 2009).

In a meta-analysis of 8 studies the sensitivity and specificity of detecting coronary artery disease by myocardial contrast stress echocardiography was 83 and 80 %, respectively. In patients with known or suspected coronary artery disease, perfusion was significantly better than wall motion analysis in detecting angiographic coronary artery stenosis, in particular at intermediate stress level (Elhendy et al., 2004). In addition, in patients with known coronary artery disease awaiting percutaneous coronary intervention, perfusion scoring was significantly better than wall motion scoring in identifying patients with prognostic significant angiographic coronary artery stenosis, like triple-vessel disease and proximal stenosis in the left anterior descending artery (Lønnebakken et al., 2009). Of note this could be achieved at intermediate stress level. Failure to achieve adequate stress level is an important limitation in assessing coronary artery disease by stress electrocardiography or stress echocardiography. It has been demonstrated that using contrast stress echocardiography with perfusion assessment (MCE) seems to overcome this limitation.

The weak association between the degree of angiographic coronary artery stenosis and quantitative myocardial perfusion by contrast stress echocardiography has been noted in several studies (Malm et al., 2006; Peltier et al., 2004; Perez et al., 2004; Lønnebakken et al., 2009). This may be explained by the fact that many other factors than coronary artery lumen diameter reduction is important for myocardial perfusion, including coronary flow autoregulation, collateral circulation, stenosis length and serial stenosis in addition to hemodynamic condition are important for myocardial perfusion. Although, mainly due to anatomic variation in coronary anatomy, contrast stress echocardiography has limited power to predict the anatomical localisation of angiographic coronary artery stenosis, the method is accurate to predict proximal stenosis in the left anterior descending coronary artery and to identify patients with multivessel disease. In addition, assessing the total ischemic burden in the individual patient may be clinically important for choosing the optimal treatment. It has been demonstrated that only patients with an ischemic burden >20% will benefit prognostically from revascularization, otherwise revascularization will only have symptomatic effect, suggesting that asymptomatic or low-symptomatic patients will have no or little effect and may be equally well off treated medically.

3.2 Acute coronary syndrome

Patients with acute coronary syndrome are a heterogeneous group with varying disease severity and prognosis, from unstable angina pectoris, non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). It is well known that both short- and long-term prognosis in NSTEMI patients is as severe as STEMI patients, although the incidence of acute coronary artery occlusions varies. It has been demonstrated that contrast echocardiography can be used for risk assessment in acute coronary syndrome patients (Senior et al., 2004; Khang et al., 2005).

3.2.1 Unstable angina pectoris

In patients hospitalized with acute chest pain but having normal serum troponin level, contrast echocardiography has been shown to be a useful tool to distinguish between patients with acute coronary syndrome and non-cardiac chest pain (Jeetley et al., 2007; Rinkevich et al., 2005; Kaul et al., 2004). Another study in 957 patients with acute chest pain and a non-diagnostic electrocardiogram demonstrated that myocardial perfusion by

contrast echocardiography was better than other commonly used risk score models like the Thrombolysis in Myocardial Infarction (TIMI) risk score (Antman et al., 2000) to discriminate between patients with intermediate or high risk for reinfarction or death (Tong et al., 2005). Based on current documentation, advanced echocardiography is underused in diagnostics and management of patients with acute chest pain.

Variables in TIMI risk score	score
Age ≥ 65 years	1
≥ 3 risk factors of CAD (family history of CAD, hypertension, diabetes, current smoking, hypercholesterolemia)	1
Prior CAD (previous MI, CABG, PCI or known angiographic stenosis $\geq 50\%$)	1
ST-segment depression ≥ 0.05 mV in ≥ 2 ECG leads	1
≥ 2 episodes of chest pain the last 24 hour	1
Aspirin the last 7 days or unfractionated heparin the last 24 hour	1
Elevated serum cardiac markers	1

Table 2. Thrombolysis In Myocardial Infarction risk score (TIMI).

3.2.2 Non-ST elevation myocardial infarction

Current guidelines for management of NSTEMI are diverging, recommending invasive risk stratification and revascularization within 12-72 hours in patients at intermediate and high risk (Bassand et al., 2007; Smith et al., 2006). In clinical risk assessment, TIMI risk score is one of the most recommended and widely used models in NSTEMI patients (Table 2). Of note, these clinical risk score models may underestimate angiographic coronary artery disease severity, in particular in patients scored as intermediate risk (Volat et al., 2008). In a recently published series of 110 patients with NSTEMI, the extent of myocardial ischemia assessed by contrast echocardiography was a better predictor of angiographic severe coronary artery disease than the TIMI risk score, in particular in identifying patients with severe disease like left main stem stenosis, trippel-vessel disease or multi-vessel disease including proximal stenosis in the left anterior descending artery and also better than wall motion scoring analysis (Fig. 7) (Lønnebakken et al., 2011). In another study in NSTEMI patients, about 30% of the patients had an acute occlusion of a main coronary artery despite normal electrocardiogram. In this study, deformation analysis by echocardiography has proven useful in identifying NSTEMI patients with severe angiographic coronary artery disease (Grenne et al., 2010). In particular serial assessment of regional left ventricular strain may identify these patients while awaiting coronary angiography and revascularisation. Theoretically, detection of these patients by either contrast echocardiography or other advanced imaging techniques represents new tools for identification of patients with high subclinical ischemic burden that may benefit from earlier revascularization.

3.2.3 ST elevation myocardial infarction

In acute STEMI the recommended treatment is immediate coronary angiography and revascularization. Contrast echocardiography can assess area at risk and help in diagnosing acute myocardial infarction in patients with acute chest pain and a non-diagnostic ECG, particularly common in patients with acute occlusion of the circumflex artery (Hayat &

Senior., 2008). But contrast echocardiography will not be indicated in pre-catheterization evaluation of most patients with STEMI.

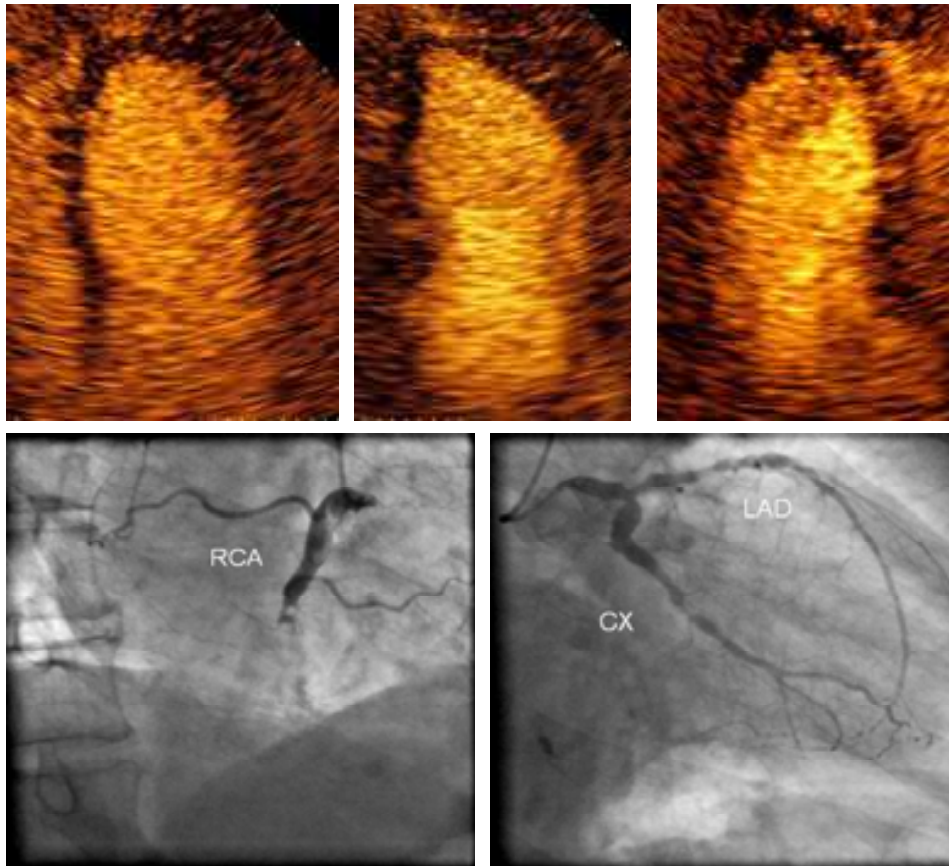


Fig. 7. Contrast echocardiography in apical 4-chamber, 2-chamber and 3-chamber views (upper panels) demonstrating the extensive reduction of myocardial perfusion in a NSTEMI patient with angiographic trippel-vessel disease including acute occlusion of the right coronary artery and left main stem stenosis (lower panels).

In spite of successful reopening of the infarct related artery by percutaneous coronary intervention, some STEMI patients still develop unexpectedly large myocardial infarctions due to the no-reflow phenomenon. The no-reflow phenomenon is caused by impaired microcirculation which can be a consequence of peripheral embolization during the percutaneous revascularization procedure or revascularisation damage due to inflammation and oedema causing microvascular obstruction and subsequent myocardial necrosis. The no-reflow phenomenon after revascularization can be diagnosed by MCE (Kaul., 2006). Lack of reperfusion after coronary intervention predicts myocardial necrosis, reduced left ventricular function, left ventricular remodelling and subsequent development of heart failure. Thus, MCE may be used in STEMI patients to identify successful reopening of the infarct related artery and to give prognostic information by identifying patients with no-reflow who need additional treatment in the acute and chronic phase of a STEMI (Dwivedi et al., 2008; Niccoli et al., 2009; Galiuto et al., 2010)

In addition to guide and evaluate treatment, an ongoing study evaluates the effect of ultrasound contrast enhanced thrombolysis in acute treatment of STEMI. The ongoing Sonolysis trial uses a combination of ultrasound induced contrast microbubbles destruction

at high mechanical index ultrasound and thrombolysis, where destruction of microbubbles causes streaming and thereby improves the effect of thrombolysis in reopening of the infarct related artery (Slikkerveer et al., 2008).

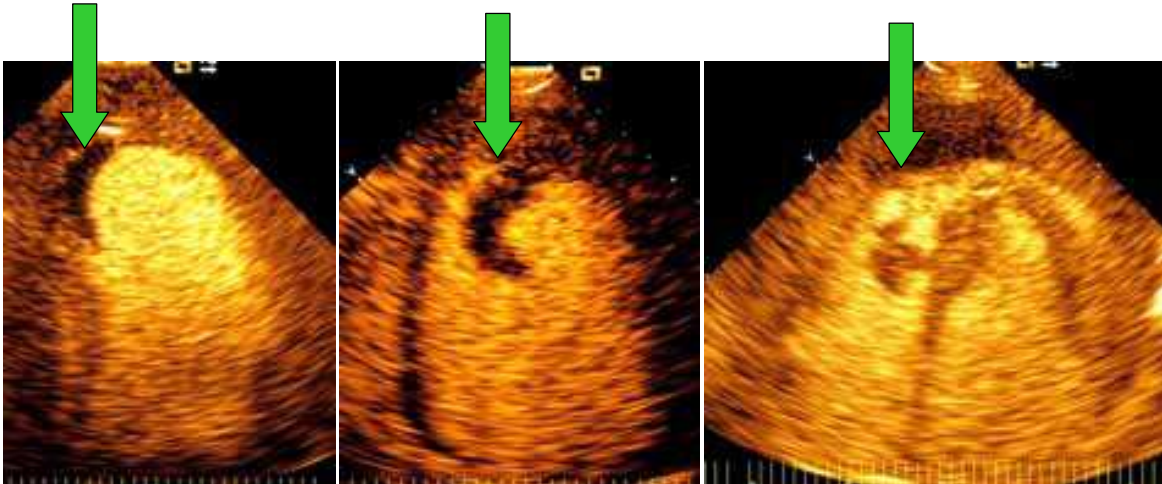


Fig. 8. Complications in acute myocardial infarction. Myocardial mural thrombus in the apex of the left ventricle, with lack of contrast enhancement due to the thrombus avascular characteristics (Panel A and B). In comparison, the typical contrast enhancement in a patient with pulmonary carcinoma and a myocardial metastasis in the right ventricle (Panel C).

Development of intraventricular mural thrombus is a feared complication to acute myocardial infarction which untreated may lead to severe thromboembolic episodes. A magnetic resonance study demonstrated that mural thrombus formation in patients with acute coronary syndromes may be more common than previously anticipated (Solheim et al., 2010). However, suspected mural thrombus may be ruled out in about 90% of patients by contrast echocardiography (Kurt et al., 2009; Hamilton-Craige et al., 2010). Diagnosing a mural thrombus with contrast echocardiography is simple and can be performed with a single ultrasound contrast bolus injection. A mural thrombus is characterized by a lack of contrast enhancement due to its avascular nature (Fig 8 Panel A and B). In contrast, a myocardial tumor is characterized by contrast enhancement which is particular high in malignant tumores that are highly vascularised structures (Fig.8 panel C).

In acute myocardial infarction, myocardial rupture is a rare and deadly complication. A rupture of the free ventricular wall is usually associated with sudden death, but occasionally, epicardial coverage occurs and subsequent formation of a ventricular pseudoaneurysm. Ventricular pseudoaneurysms can be difficult to diagnose by conventional echocardiography (Fig. 9 left panel), but are easy to recognize after injection of an ultrasound contrast agent during imaging (Fig. 9 right panel).

3.3 Restenosis after revascularization

In patients undergoing percutaneous coronary intervention with stent implantation, 10-30% will develop significant angiographic restenosis in spite of initial successful treatment. Restenosis is caused by intimal hyperplasia and is asymptomatic in 50% of patients (Giedd & Bergmann., 2004). However, even in asymptomatic patients development of restenosis is associated with a poorer prognosis (Pfisterer et al., 1993; Zellweger et al., 2003). Non-

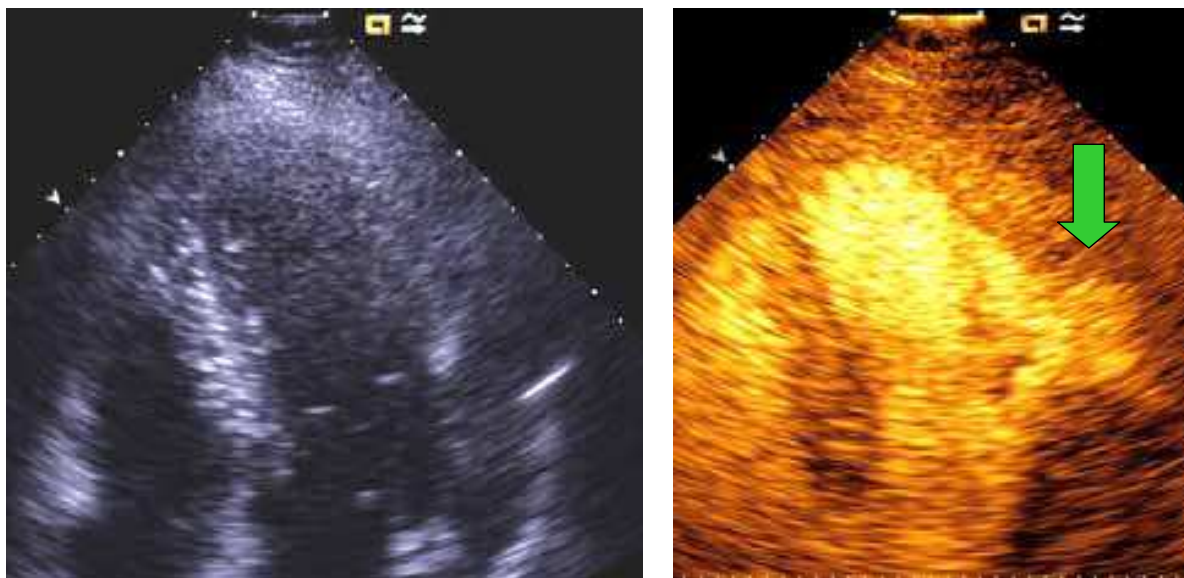


Fig. 9. Extracardial contrast enhancement due to a pseudoaneurysm in the lateral wall of the left ventricle (right panel) not visible with conventional echocardiography (left panel).

invasive diagnosis of restenosis can be challenging. Previous SPECT studies have demonstrated that normalization of regional myocardial perfusion usually occurs after successful revascularization (Manyari et al., 1988; Zhang et al., 2004). In a follow-up study using quantitative contrast stress echocardiography in 33 patients with stable angina pectoris treated with percutaneous coronary intervention and stent implantation, there was no improvement in stress-induced myocardial perfusion during follow-up in patients who had developed a significant angiographic restenosis, while the stress-induced perfusion was improved in patients with successful revascularisation at 9 months (Lønnebakken et al., 2009).

At present, quantitative contrast stress echocardiography is not recommended in routine assessment of coronary artery disease due to inter-individual variation and lack of data on normal values and cut-off values indicating ischemia for this method. Still, serial assessment in individual patients may be useful.

3.4 Non-obstructive coronary artery disease

Although coronary angiography remains the gold standard for diagnosis of coronary artery disease, it should be kept in mind that myocardial ischemia may be present in spite of angiographically open epicardial coronary arteries, a condition known as non-obstructive ischemic heart disease. This condition cannot be diagnosed using angiography alone, but requires additional use of perfusion assessment with cardiac magnetic resonance or MCE. In patients with acute coronary syndrome, non-obstructive ischemic heart disease is present in 15% of women and 9% of men (Berger et al., 2009). Cardiac magnetic resonance studies in NSTEMI patients have demonstrated myocardial infarction in up to 34% of patients with normal coronary arteries by coronary angiography. Clot autolysis and recanalisation of the infarct related artery are the main reasons for this finding as well as microvascular disease that can not be detected by coronary angiography, the current diagnostic gold standard. In patients with recurrent hospitalisation for chest pain and “normal” coronary arteries by coronary angiography additional non-invasive cardiac imaging should be performed. MCE

can be used to diagnose myocardial ischemia in such patients and thereby distinguish between patients with non-cardiac chest pain and patients with non-obstructive ischemic heart disease. Non-obstructive ischemic heart disease most often is caused by microvascular disease associated with diabetes mellitus, obesity and hypertension, but also hemodynamic changes like increased left ventricular filling pressure and increased arterial stiffness can cause reduced myocardial perfusion pressure and hence myocardial ischemia despite angiographically normal epicardial coronary arteries (London et al., 2004). Chronic myocardial ischemia in such patients may promote development of myocardial fibrosis and secondary structural changes in the left ventricle, finally leading to functional impairment and heart failure (Niccoli et al., 2009).

Another recently recognized condition mainly affecting women is the Takotsubo cardiomyopathy, mimicking an acute myocardial infarction. The exact pathophysiological mechanism remains unknown in Takotsubo cardiomyopathy, but it involves myocardial hypoperfusion that can be diagnosed by contrast echocardiography causing functional impairment mainly in the apical part of the left ventricle with the characteristic apical ballooning (Fig. 10) (Abdelmoneim et al., 2009). The microvascular involvement is also confirmed by early cardiac MRI demonstrating late gadolinium uptake suggesting diffuse microcirculation damage (Avegliano et al., 2011).

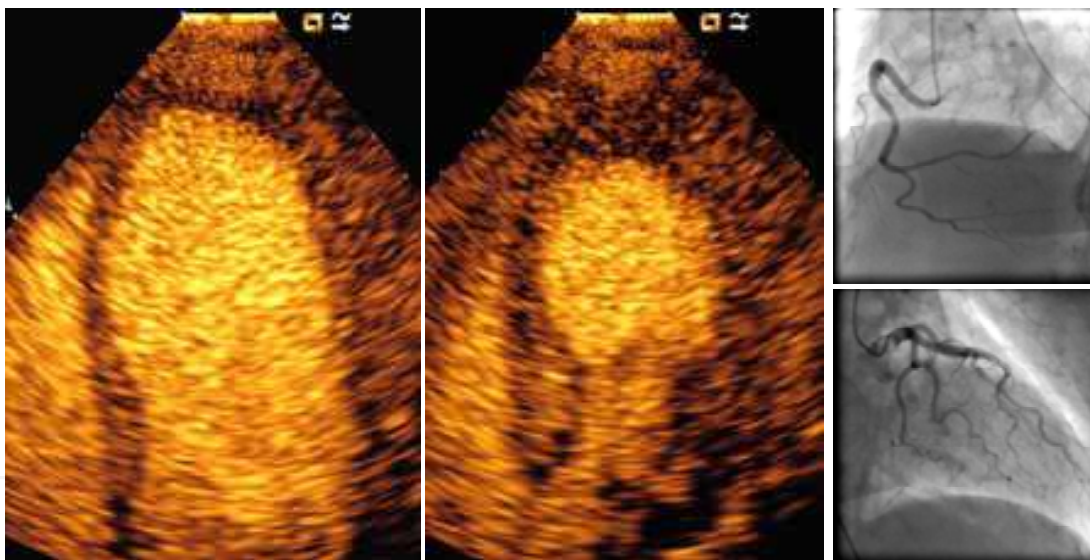


Fig. 10. Takotsubo Cardiomyopathy. Contrast echocardiography in diastole and systole illustrating the apical akinesia and ballooning of the left ventricle in an apical 4-chamber view, in addition there is a delayed contrast enhancement in the apical segments of the left ventricle. The right panel shows the normal coronary angiogram confirming the diagnosis Takotsubo cardiomyopathy.

4. Conclusion

Contrast echocardiography allows simultaneous assessment of regional myocardial function and perfusion, improving non-invasive diagnosis and assessment of coronary artery disease. Contrast echocardiography gives information on the physiological impact of the coronary artery stenosis, reveals the ischemic burden, detects viable myocardium and may

act as a supplemental tool to coronary angiography in management of coronary artery disease and in follow-up after treatment. In addition, the ability to diagnose myocardial ischemia in patients with no-reflow phenomenon or microvascular disease and angiographically normal coronary arteries may help distinguishing patients with non-obstructive ischemic coronary artery disease from patients with non-cardiac chest pain. Future studies using targeted contrast microbubbles against specific disease processes may further improve diagnosis in ischemic coronary artery disease, and on-going studies explore the use of ultrasound contrast agents to potentiate the effect of thrombolysis in acute coronary artery occlusions.

5. References

- Abdelmoneim SS, Dhoble A, Bernier M, Erwin PJ, Korosoglou G, Senior R, Moir S, Kowatsch I, Xian-Hong S, Muro T, Dawson D, Vogel R, Wei K, West CP, Montori VM, Pellikka PA, Abdel-Kader SS & Mulvagh SL. (2009) Quantitative myocardial contrast echocardiography during pharmacological stress for diagnosis of coronary artery disease: a systematic review and meta-analysis of diagnostic accuracy studies. *Eur JEchocardiogr* 2009;10(7):813-825
- Abdelmoneim SS, Mankad SV, Bernier M, Dhoble A, Hagen ME, Ness SA, Chandrasekaran K, Pellikka PA, Oh JK & Mulvagh SL. (2009). Microvascular function in Takotsubo cardiomyopathy with contrast echocardiography: prospective evaluation and review of literature. *JAm Soc Echocardiogr* . 2009;22:1249-55.
- Agati L, Tonti G, Galiuto L, Di Bello V, Funaro S, Madonna MP, Garramone B & Magri T, A.M.I.C.I Investigators. (2005). Quantification methods in contrast echocardiography. *Eur JEchocardiogr* 2005;6 Suppl 2:S14-20.
- Antman EM, Cohen M, Bernink PJ, Mc Cabe CH, Horacek T, Papuchis G, Mauntner B, Corbalan R, Radley D & Braunwald El. (2000). The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
- Avegeliano G, Huguet M, Costabel JP, Ronderos R, Bijmens B, Kuschnir P, Thierer J, Tob\on-Gomez C, Martinez GO & Frangi A. (2011) Morphologic pattern of late gadolinium enhancement in takotsubo cardiomyopathy detected by early cardiovascular magnetic resonance. *Clin. Cardiol.* 2011; 34:178-82.
- Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L & Wijns W. (2007) Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28(13):1598-1660.
- Berger JS, Elliott L, Gallup D, RoeM, Granger CB, Armstrong PW, Simes RJ, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC & Douglas PS. (2009) Sex differences in mortality following acute coronary syndromes. *JAMA* 2009; 302:874-82.
- Chadderdon SM & Kaul S. Molecular imaging with contrast enhanced ultrasound. (2010) *J Nucl Cardiol* 2010; 17:667-77.
- Chahal NS & Senior R. Clinical applications of left ventricular opacification. (2010) *JACC Cardiovasc Imaging* 2010; 3:188-96.

- Crossman DC. (2004) The pathophysiology of myocardial ischaemia. *Heart* 2004;90(5):576-580.
- Dijkmans PA, Senior R, Becher H, Porter TR, Wei K, Visser CA & Kamp O. (2006). Myocardial contrast echocardiography evolving as a clinically feasible technique for accurate, rapid, and safe assessment of myocardial perfusion: the evidence so far. *J Am Coll Cardiol* 2006;48(11):2168-2177.
- Dwivedi G, Janardhanan R, Hayat SA, Lim TK, Greaves K & Senior R. (2008) Relationship between myocardial perfusion with myocardial contrast echocardiography and function early after acute myocardial infarction for the prediction of late recovery of function. *Int JCardiol* 2008.
- Elhendy A, O'Leary EL, Xie F, McGrain AC, Anderson JR & Porter TR. (2004). Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. *JAm Coll Cardiol* 2004;44(11):2185-2191.
- Elhendy A & Porter TR. (2005) Assessment of myocardial perfusion with real-time myocardial contrast echocardiography: methodology and clinical applications. *J Nucl Cardiol* 2005;12(5):582-590.
- Galiuto L, Paraggio L, Liuzzo G, de Caterina AR & Crea F. (2010) Predicting the no-reflow phenomenon following successful percutaneous coronary intervention. *Biomark. Med.* 2010; 4:403-20.
- Giedd KN & Bergmann SR.(2004) Myocardial perfusion imaging following percutaneous coronary intervention: the importance of restenosis, disease progression, and directed reintervention. *JAm Coll Cardiol* 2004;43(3):328-336.
- Grenne B, Eek C, Sjøli B, Dahlslett T, Uchto M, Hol PK, Skulstad H, Smiseth OA, Edvardsen T & Brunvand H. (2010) Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. *Heart* 2010; 96:1550-6.
- Hamilton-Craig C, Boga T, West C, Kelly N, Anscombe R, Burstow D & Platts D. (2010) Contrast echocardiography in Australian clinical practise. *Heart Lung Circ* 2010; 19:385-94.
- Hayat SA & Senior R. (2008) Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J*2008; 29:299-314.
- Hoffmann R, Borges AC, Kasprzak JD, von BS, Firschke C, Greis C, Engelhardt M, Becher H & Vanoverschelde JL.(2007) Analysis of myocardial perfusion or myocardial function for detection of regional myocardial abnormalities. An echocardiographic multicenter comparison study using myocardial contrast echocardiography and 2D echocardiography. *Eur JEchocardiogr* 2007;8(6):438-448.
- Jeetley P, Burden L, Greaves K & Senior R. (2007). Prognostic value of myocardial contrast echocardiography in patients presenting to hospital with acute chest pain and negative troponin. *Am JCardiol* 2007;99(10):1369-1373.
- Kaufmann BA & Lindner JR.(2007) Molecular imaging with targeted contrast ultrasound. *Curr Opin Biotechnol* 2007;18(1):11-16.
- Kaul S, Senior R, Firschke C, Wang XQ, Lindner J, Villanueva FS, Firozan S, Kontos MC, Taylor A, Nixon IJ, Watson DD & Harrell FE. (2004) Incremental value of cardiac

- imaging in patients presenting to the emergency department with chest pain and without ST-segment elevation: a multicenter study. *Am Heart J* 2004;148(1):129-136.
- Kaul S. (2006) Evaluating the 'no reflow' phenomenon with myocardial contrast echocardiography. *Basic Res Cardiol* 2006;101(5):391-399.
- Kang DH, Kang SJ, Song JM, Choi KJ, Hong MK, Song JK, Park SW & Park SJ. (2005) Efficacy of myocardial contrast echocardiography in the diagnosis and risk stratification of acute coronary syndrome. *Am J Cardiol* 2005;96(11):1498-1502.
- Kurt M, Shaikh KA, Peterson L, Kurrelmeyer KM, Shah G, Nagueh SF, Fromm R, Quinones MA & Zoghbi WA. (2009) Impact of contrast echocardiography on evaluation of ventricular function and clinical management in a large prospective cohort. *J Am Coll Cardiol*. 2009;3:802-10.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John SM & Stewart W. (2006) Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7(2):79-108.
- Leong-Poi H, Rim SJ, Le DE, Fisher NG, Wei K & Kaul S. (2002) Perfusion versus function: the ischemic cascade in demand ischemia: implications of single-vessel versus multivessel stenosis. *Circulation* 2002;105(8):987-992.
- London GM, Marchais SJ, Guerin AP & Pannier B. (2004) Arterial stiffness : pathophysiology and clinical impact. *Clin Exp Hypertens* 2004;26:689-99.
- Lønnebakken MT, Bleie Ø, Strand E, Staal EM, Nygård OK & Gerdt E. (2009) Myocardial contrast echocardiography in assessment of stable coronary artery disease at intermediate dobutamine-induced stress level *Echocardiography* 2009;26:52-60.
- Lønnebakken MT, Staal EM, Bleie Ø, Strand E, Nygård OK & Gerdt E. (2009). Quantitative contrast stress echocardiography in assessment of restenosis after percutaneous coronary intervention in stable coronary artery disease. *Eur J Echocardiogr*. 2009; 10:858-64.
- Lønnebakken MT, Staal EM, Nordrehaug JE & Gerdt E. (2011) Usefulness of contrast echocardiography for predicting the severity of angiographic coronary disease in non-ST-elevation myocardial infarction. *Am J Cardiol* 2011, feb 22 (e-pub ahead of print)
- Malm S, Frigstad S, Helland F, Oye K, Slordahl S & Skjarpe T. (2005) Quantification of resting myocardial blood flow velocity in normal humans using real-time contrast echocardiography. A feasibility study. *Cardiovasc Ultrasound* 2005;3:16.
- Malm S, Frigstad S, Sagberg E, Steen PA & Skjarpe T. (2006) Real-time simultaneous triplan contrast echocardiography gives rapid, accurate, and reproducible assessment of left ventricular volumes and ejection fraction: a comparison with magnetic resonance imaging. *J Am Soc Echocardiogr*. 2006; 19:1494-501.
- Malm S, Frigstad S, Torp H, Wiseth R & Skjarpe T. (2006) Quantitative adenosine real-time myocardial contrast echocardiography for detection of angiographically significant coronary artery disease. *J Am Soc Echocardiogr* 2006;19(4):365-372.
- Manyari DE, Knudtson M, Kloiber R & Roth D. (1988) Sequential thallium-201 myocardial perfusion studies after successful percutaneous transluminal coronary artery angioplasty: delayed resolution of exercise-induced scintigraphic abnormalities. *Circulation* 1988;77(1):86-95.

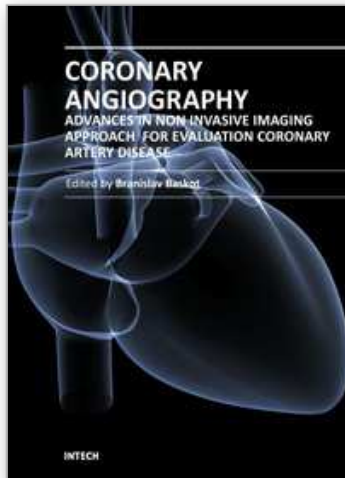
- Mollema SA, Nucifora GV, Bax JJ. (2009) Prognostic value of echocardiography after acute myocardial infarction. *Heart* 2009;95(21):1732-1745.
- Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, Burns PN, Castello R, Coon PD, Hagen ME, Jollis JG, Kimball TR, Kitzman DW, Kronzon I, Labovitz AJ, Lang RM, Mathew J, Moir WS, Nagueh SF, Pearlman AS, Perez JE, Porter TR, Rosenbloom J, Strachan GM, Thanigaraj S, Wei K, Woo A, Yu EH & Zoghbi WA. (2008) American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr* 2008;21(11):1179-1201.
- Niccoli G, Burzotta F, Galiuto L & Crea F. (2009) Myocardial no-reflow in humans. *J Am Coll Cardiol* 2009; 54:281-92.
- Peltier M, Vancraeynest D, Pasquet A, Ay T, Roelants V, D'hondt AM, Melin JA & Vanoverschelde JL. (2004) Assessment of the physiologic significance of coronary disease with dipyridamole real-time myocardial contrast echocardiography. Comparison with technetium-99m sestamibi single-photon emission computed tomography and quantitative coronary angiography. *J Am Coll Cardiol* 2004;43(2):257-264.
- Perez d, I, Rodrigo JL, Almeria C, Perez FM, Serra V & Zamorano JL. (2004) Myocardial contrast echocardiography in coronary artery disease. *Eur J Echocardiogr* 2004;5 Suppl 2:S11-S16.
- Pfisterer M, Rickenbacher P, Kiowski W, Müller-Brand J & Burkart F. (1993). Silent ischemia after percutaneous transluminal coronary angioplasty: incidence and prognostic significance. *J Am Coll Cardiol* 1993;22(5):1446-1454.
- Picano E, Molinaro S & Pasanisi E. (2008) The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound* 2008;6:30.
- Plana JC, Mikati IA, Dokainish H, Lakkis N, Abukhalil J, Davis R, Hetzell BC & Zoghbi WA. (2008) A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. *JACC Cardiovasc Imaging* 2008; 1:145-52.
- Rinkevich D, Kaul S, Wang XQ, Tong KL, Belcik T, Kalvaitis S, Lepper W, Dent JM & Wei K. (2005) Regional left ventricular perfusion and function in patients presenting to the emergency department with chest pain and no ST-segment elevation. *Eur Heart J* 2005;26(16):1606-1611.
- Senior R, Villanueva F & Vannan MA. (2004) Myocardial contrast echocardiography in acute coronary syndromes. *Cardiol Clin* 2004;22(2):253-267
- Senior R, Monaghan M, Becher H, Mayet J & Nihoyannopoulos P. (2005) Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography. *Heart* 2005;91(4):427-436.
- Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL & Nihoyannopoulos P. (2009). Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. *Eur JEchocardiogr* 2009;10(2):194-212.

- Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU & Zamorano JL. (2008) Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr.* 2008;9(4):415-437.
- Slikkerveer J, Dijkmans PA, Sieswerda GT, Doevendans PA, van Dijk AP, Verheugt FW, Porter TR & Kamp O. (2008) Ultrasound enhanced thrombolysis using microbubbles infusion in patients with acute ST elevation myocardial infarction: rationale and design of the Sonolysis study. *Trials* 2008; 9:72.
- Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr. Jacobs AK, Kern MJ, King SB, III, Morrison A, O'Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL & Riegel B. (2006). ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113(7):e166-e286.
- Solheim S, Seljeflot I, Lunde K, Bjørnerheim R, Aakhus S, Forfang K & Arnesen H. (2010) Frequency of left ventricular thrombus in patients with anterior wall acute myocardial infarction treated with percutaneous coronary intervention and dual antiplatelet therapy. *Am J Cardiol.* 2010;106:1197-200.
- Toledo E, Jacobs LD, Lodato JA, DeCara JM, Coon P, Mor-Avi V & Lang RM. (2006) Quantitative diagnosis of stress-induced myocardial ischemia using analysis of contrast echocardiographic parametric perfusion images. *Eur J Echocardiogr* 2006;7(3):217-225.
- Tong KL, Kaul S, Wang XQ, Rinkevich D, Kalvaitis S, Belcik T, Lepper W, Foster WA & Wei K. (2005). Myocardial contrast echocardiography versus Thrombolysis In Myocardial Infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. *J Am Coll Cardiol.* 2005; 46:920-7.
- Vorlat A, Claeys MJ, De RH, Gevaert S, Vandekerckhove Y, Dubois P, De MA & Vrints C. (2008). TIMI risk score underestimates prognosis in unstable angina/non-ST segment elevation myocardial infarction. *Acute Card Care* 2008;10(1):26-29.
- Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM & Kaul S.(1998). Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation* 1998;97(5):473-483.
- Wei K, Mulvagh SL, Carson L, Davidoff R, Gabriel R, Grimm RA, Wilson S, Fane L, Herzog CA, Zoghbi WA, Taylor R, Farrar M, Chaudhry FA, Porter TR, Irani W & Lang RM. (2008) The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. *J Am Soc Echocardiogr* 2008;21(11):1202-1206.
- Zellweger MJ, Weinbacher M, Zutter AW, Jeger RV, Mueller-Brand J, Kaiser C, Buser PT & Pfisterer ME. (2003). Long-term outcome of patients with silent versus symptomatic ischemia six months after percutaneous coronary intervention and stenting. *J Am Coll Cardiol* 2003;42(1):33-40.

Zhang X, Liu X, He ZX, Shi R, Yang M, Gao R, Chen J, Yang Y & Fang W. (2004) Long-term prognostic value of exercise ^{99m}Tc -MIBI SPET myocardial perfusion imaging in patients after percutaneous coronary intervention. *Eur J Nucl Med Mol Imaging* 2004;31(5):655-662.

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In the intervening 10 years tremendous advances in the field of cardiac computed tomography have occurred. We now can legitimately claim that computed tomography angiography (CTA) of the coronary arteries is available. In the evaluation of patients with suspected coronary artery disease (CAD), many guidelines today consider CTA an alternative to stress testing. The use of CTA in primary prevention patients is more controversial in considering diagnostic test interpretation in populations with a low prevalence to disease. However the nuclear technique most frequently used by cardiologists is myocardial perfusion imaging (MPI). The combination of a nuclear camera with CTA allows for the attainment of coronary anatomic, cardiac function and MPI from one piece of equipment. PET/SPECT cameras can now assess perfusion, function, and metabolism. Assessing cardiac viability is now fairly routine with these enhancements to cardiac imaging. This issue is full of important information that every cardiologist needs to now.

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